CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761178Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 7, 2021
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Ancy Nalli, PhD, Product Quality Assessor Haoheng Yan, MD. Ph.D Team Leader OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761178
Applicant:	Biogen Inc.
Submission Date:	July 20, 2020
Product:	Aduhelm (aducanumab-avwa)
Dosage form(s):	injection
Strength and Container-Closure:	170 mg/1.7 mL (100 mg/mL) in a single-dose vial 300 mg/3 mL (100 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information (submitted on June 7, 2021), medication guide (submitted on June 4, 2021), container labels (submitted on October 9, 2020), and carton labeling (submitted on October 30, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information (submitted on June 7, 2021), medication guide (submitted on June 4, 2021), container labels (submitted on October 9, 2020), and carton labeling (submitted on October 30, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

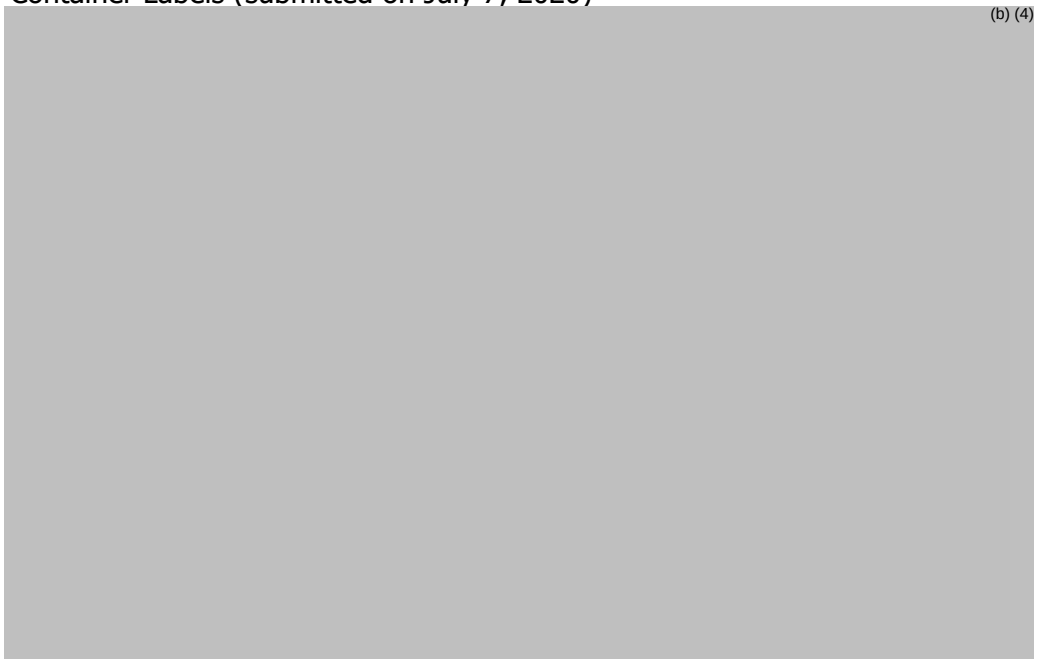
APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on July 7, 2020
\\CDSESUB1\evsprod\bla761178\0003\m1\us\draft-labeling-uspi-20200624.doc)

Medication Guide (submitted on July 7, 2020
\\CDSESUB1\evsprod\bla761178\0003\m1\us\draft-labeling-mg-20200624.doc)

Container Labels (submitted on July 7, 2020)



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *Biogen confirms there is no text on the ferrule and cap overseal of the vials.*

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located. *Biogen confirms there is sufficient area of the container remaining uncovered as indicated by the transparent window.*

	(b) (4)		(b) (4)

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Since your product is light sensitive, providing instructions on how to protect from light may be helpful for the end user. Consider revising the storage statement from (b) (4) to "**STORAGE:** Store in original carton to protect from light until use."
The Applicant revised as requested

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the ingredient list to match your prescribing information. The inactive ingredient amounts were revised to two decimal places and relocated to appear in parenthesis after the name to separate the active ingredient from the inactive ingredients as follows: "Each single-dose vial contains [170 mg/1.7 mL or 300 mg/3 mL] of Aduhelm. Each mL of solution contains 100 mg of aducanumab-avwa, and L-arginine hydrochloride (31. (b)(4) mg), L-histidine (0. (b)(4) mg), L-histidine hydrochloride monohydrate (3.39 mg), L-methionine (1.49 mg), polysorbate 80 (0.50 mg), and Water for Injection.

Biogen has updated the ingredient list to the following: "Each single-dose vial contains [170 mg/1.7 mL or 300 mg/3 mL] of Aduhelm. Each mL of solution contains 100 mg of aducanumab-avwa, and L-arginine hydrochloride (31.60 mg), L-histidine (0.60 mg), L-histidine hydrochloride monohydrate (3.39 mg), L-methionine (1.49 mg), polysorbate 80 (0.50 mg), and Water for Injection."

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic; USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the statement of dosage to "Dosage: See Prescribing Information"
The Applicant revised as requested

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. Revise from (b) (4) to either "ATTENTION: Dispense the enclosed Medication Guide to Each Patient" or "Always Dispense the enclosed Medication Guide to Each Patient".

Biogen has updated this statement to "ATTENTION: Dispense the enclosed Medication Guide to Each Patient."

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Since your product is light sensitive and photostability data have not been submitted to the BLA to support stability of the diluted product under light conditions, instructions to protect the diluted solution from light have been added.

The Applicant proposes to remove "protected from light" based on data collected to support no impact of light exposure after dilution for up to 12 hours per sub-section 1.5 of 3.2.P.2.6

OBP PQ confirmed data support this revision

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: (b) (4) has been removed and recommend that if this information is needed (b) (4)

The Applicant has removed (b) (4)

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: (b) (4) has been deleted from the first paragraph (b) (4)

The Applicant revised as requested

Revised to kDa as a customary presentation of MW

The Applicant revised as requested

The concentration and supplied strengths are provided for clarity

The Applicant revised as requested

Revised to relocate the inactive ingredient amounts in parenthesis after the name to separate the active ingredient from the inactive ingredients

The Applicant revised as requested

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16:	☐ Yes ☐ No ☒ N/A

xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Stability data support storage at RT for up to 24 hours while protected from light thus revised to "Prior to dilution, unopened vials of ADUHELM can be removed from and returned to the refrigerator if necessary when kept in the original carton. Total combined time out of refrigeration with protection from light should not exceed 24 hours at room temperature"
The Applicant revised as requested

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling
Prescribing Information (submitted on June 7, 2021
\\CDSESUB1\evsprod\bla761178\0090\m1\us\draft-labeling-uspi-20210606.doc)
Medication Guide (submitted on June 4, 2021
\\CDSESUB1\evsprod\bla761178\0089\m1\us\draft-labeling-mg-20210604.doc)

Container Labels (submitted on October 9, 2020)

(b) (4)

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Vicky Borders-Hemphill

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Ancy Nalli

Digitally signed by Ancy Nalli
Date: 6/07/2021 12:00:43PM
GUID: 5c6ebeb30003b37749b660cdb6d9dfe9

Haoheng Yan

Digitally signed by Haoheng Yan
Date: 6/07/2021 11:53:17AM
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BLA 761178 Quality Assessment
ADUHELM (Aducanumab-avwa)

Manufacturer: Biogen Inc.

Rukman De Silva: Drug Substance, Validation of Analytical Methods
Ancy Nalli: Drug Product
Frederick Mills: Immunogenicity
Thomas O'Connor, DPQR/OTR, FDA Emerging Technology Team: Process Analytical Tool
Haoheng Yan: Application Technical Lead

Division of Biotechnology Review and Research IV
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP Product Quality Assessment Data Sheet

1. BLA#: 761178
2. Assessment Date: 5/21/2021
3. Primary Assessment Team:

Discipline/Organization	Names	
Regulatory Project Management	RPM:	E. Andrew Papanastasiou
	CPMS/TL:	Heather Bullock
Cross-Discipline Team Leader (CDTL)	Ranjit Mani	
Division Director/Deputy	Eric Bastings – Director Teresa Buracchio – Deputy Director	
Office Director/Deputy	Billy Dunn	
Clinical	Reviewer:	Kevin Krudys - Efficacy Brian Trummer – ARIA (safety)
	TL:	Ranjit Mani
Safety	Reviewer:	Natalie Branagan
	TL:	Sally Jo Yasuda
Clinical Pharmacology	Reviewer:	Gopichand Gottipati
	TL:	Sabarinath (Sab) Sreedharan
Pharmacometrics	Reviewer:	Michael Bewernitz
	Reviewer:	Vishnu Sharma
	TL:	Atul Bhattaram
Biostatistics	Reviewer:	Tristan Massie
	TL:	Kun Jin
	Leadership	Hsien Ming (Jim) Hung Sue Jane Wang
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Hawver
	TL:	Lois Freed
Product Quality (CMC) Review Team:	ATL:	Haoheng Yan
	RBPM:	Rabiya Haider
Drug Substance Drug Product	Reviewer:	Rukman De Silva Ancy Nalli

Immunogenicity Labeling		Frederick Mills Vicky Borders-Hemphill
Microbiology Reviewers	Reviewer:	Candace Gomez-Broughton
	Reviewer:	Wendy Tan
Facilities	Reviewer:	Zhong Li
	TL:	Thuy Thanh Nguyen
Bioresearch Monitoring (OSI)	Reviewer:	Cara Alfaro
	TL:	Philip Kronstein

4. Major GRMP Deadlines:
    a. Filing Meeting: 7/22/2020
    b. Mid-cycle meeting: 9/29/2020
    c. Advisory committee meeting: 11/6/2020
    d. Late-cycle meeting: 12/08/2020 and 05/11/2021
    f. PDUFA action date: extended to 6/7/2021

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request # 1	7/30/2020
Information Request # 2	10/9/2020
Information Request # 3	10/14/2020
Information Request # 4	10/23/2020
Information Request # 5	11/2/2020
Information Request # 6	11/6/2020
Information Request # 7	11/19/2020
Information Request # 8	11/19/2020
Information Request # 9	5/14/2021
Information Request # 10	5/21/2021

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (yes or no)
0002 (original submission)	5/15/2020	Yes
0016 (response to IR #1)	8/11/2020	Yes
0040 (response to IR #2)	10/16/2020	Yes
0040 (response to IR #3)	10/16/2020	Yes
0043 (response to IR #4)	10/28/2020	Yes
0050 (response to IR #5)	11/04/2020	Yes
0053 (response to IR #6)	11/09/2020	Yes
0055 (response to IR #7)	11/23/2020	Yes
0059 (response to IR #8)	12/02/2020	Yes
0073 (response to IR#9)	05/17/2021	Yes

0080 (response to IR #10)	05/27/2021	Yes

7. Drug Product Name/Code/Type:
   a. Proprietary Name: ADUHELM
   b. Trade Name: ADUHELM
   c. Non-Proprietary Name/USAN/INN: Aducanumab-avwa
   d. CAS Name: 1384260-65-4
   e. Common Name: None
   f. Compendial Name: None
   g. OBP systematic name: MAB HUMAN (IGG1) ANTI P05067 (A4_HUMAN) [BIIB037]
   h. Other Name: BIIB037 (company code)

8. Pharmacological Category: Recombinant IgG1 monoclonal antibody directed against human amyloid beta.
9. Dosage Form: Injection in a single-dose vial with flip cap

10. Strength/Potency:

170 mg/1.7 mL (100 mg/mL)
300 mg/3 mL (100 mg/mL)
The applicant proposes to market 170mg and 300mg strengths only in the original submission.

Product quality information for the following strength was also provided and reviewed.
(b) (4)

11. Route of Administration: Intravenous (IV) infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	Defer to OPMA reviewer
			Yes	Adequate information was submitted in the
			Yes	

(b) (4)	Yes	BLA. No need to review the DMF
	Yes	(b) (4) Please see assessor's comments in the review section 3.2.A.2.

13. Inspectional Activities:
Drug Substance Facility:
In lieu of a pre-license on-site inspection (PLI) for the drug substance manufacturing facility Biogen MA Inc. (referred to as Biogen RTP) (FEI 3000719749), a review of manufacturing site records under Section 704(a)(4) was conducted and found adequate. The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761178.

Drug Product Facility:
PLI to the two DP facilities (listed below) were waived the firm's compliance history, current acceptable cGMP status, (b) (4) .

Biogen U.S. Corporation (Biogen RTP-PF)
900 Davis Drive, Research Triangle Park, NC 27709, USA
FEI # 3010164829

(b) (4)

14. Consults Requested by OBP:
A consult request was sent to OTR to review following PAT elements (b) (4):
(b) (4)

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control

x	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

A. Signature Block

Name and Title	Signature and Date
Haoheng Yan, MD. Ph.D. Team Leader Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
Rukman De Silva, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

I recommend approval of BLA 761178 application for ADUHELM (Aducanumab-avwa). The data submitted in the BLA demonstrate the manufacturing process of aducanumab is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process were adequately validated, and the product was consistently manufactured from multiple production runs.

II. List of Deficiencies to be Communicated

There are no CMC-related deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments/Requirements

- *Implement a validated product-specific host cell protein (HCP) assay in aducanumab drug substance manufacturing process. Submit the HCP method and method validation report in a supplement within 9 months of licensure.*
- *Perform commercial shipping qualification studies for drug product and finished goods, and submit reports in a supplement within 8 months of licensure.*
- *As discussed in the FDA 2019 guidance for immunogenicity assays, matrix effects arising from hemolysis and lipidemia have the potential to interfere with anti-drug antibody (ADA) assays. In this regard, we note that there was an approximate 19% incidence of both hyperlipidemia and hypercholestrolemia in your Phase 3 studies (Summary Clinical Safety m.2.7.4), and these conditions make it more likely that there will be interfering lipids in ADA samples. Therefore, we ask that you evaluate the potential for matrix*

interference from hemolysis and lipidemia in your ADA assay as a Post Marketing Commitment.

IV. Assessment of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion
Biogen claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria per 21 CFR Part 25.31(c). The request for categorical exclusion is acceptable.

V. Primary Container Labeling Assessment
The CMC labeling review was performed by Vicky Borders-Hemphill, CDER/OPQ/OBP. The review memo is uploaded to Panorama separately.

VI. Assessment of Common Technical Document- Quality Module 3.2
3.2.S. Drug Substance, 3.2.A Adventitious Agents Safety Evaluation and 3.2.R Regional information (method validation reports) are reviewed by Rukman De Silva and the review assessment is included in this review memorandum. 3.2.P. Drug Product: reviewed by Ancy Nalli and the review memo is uploaded to Panorama separately.

VII. Assessment of Immunogenicity Assays- Module 5.3.1.4
The immunogenicity assays were reviewed by Frederick Mills, CDER/OPQ/OBP. Refer to review by Frederick Mills in Panorama.

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Rukman De Silva

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Haoheng Yan

Digitally signed by Haoheng Yan
Date: 6/02/2021 10:57:21AM
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First Approval for Indication/Accelerated Approval

Recommendation: Approval

BLA/NDA Number: 761178
Review Number: 1
Review Date: 5/20/2021

Drug Name/Dosage Form	Aduhelm, Aducanumab-avwa
Strength/Potency	Vial: 170 mg/1.7 mL and 300 mg/3 mL (100 mg/mL)
Route of Administration	Intravenous (IV)
Rx/OTC dispensed	Rx
Indication	delay clinical decline in patients with Alzheimer's disease
Applicant	Biogen

Product Overview:

Aducanumab-avwa is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody targeting aggregated soluble and insoluble forms of amyloid beta. It is expressed in a Chinese hamster ovary (CHO) cell line.

ADUHELM (aducanumab-avwa) injection is a preservative-free, sterile, clear to opalescent and colorless to yellow solution for intravenous infusion after dilution. It is supplied in single-dose vials available in concentrations of 170 mg/1.7 mL (100 mg/mL) or 300 mg/3 mL (100 mg/mL).

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Rukman De Silva	Division of Biotechnology Review and Research (DBRR) IV
Drug Product (DP)	Ancy Nalli	DBRR IV
Immunogenicity	Frederick Mills	DBRR IV
Labeling	Vicky Borders-Hemphill	Office of Biotechnology Products (OBP)
Facility	Zhong Li	Office of Pharmaceutical Manufacturing Assessment/ Division of Biotechnology Manufacturing (OPMA) OPMA/DBM
Facility Team Lead	Thuy Thanh Nguyen	OPMA/DBM
Microbiology	Wendy Tan	OPMA/DBM
Microbiology Team Lead	Candace Gomez-Broughton	OPMA/DBM
Application Team Lead	Haoheng Yan	DBRR IV
RBPM	Rabiya Haider	Office of Program and Regulatory Operations (OPRO)

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	E. Andrew Papanastasiou	OND/ORO/DRON
Cross-disciplinary Team Lead	Ranjit Mani	OND/ON/DNI
Medical Officer	Kevin Krudys - Efficacy Brian Trummer – ARIA (safety)	OND/OOD/DOI
Pharmacology/Toxicology	David Hawver/ Lois Freed	OND/DPTN
Clinical Pharmacology	Gopichand Gottipati/ Sabarinath (Sab) Sreedharan	OTS/OCP/DMP
Statistics	Tristan Massie/ Kun Jin	OTS/OB/DBI

Names:

a. Proprietary Name: ADUHELM
b. Trade Name: ADUHELM
c. Non-Proprietary Name/USAN: Aducanumab-avwa
d. CAS Registry Number: 1384260-65-4
e. Common Name: BIIB037 (company code)
f. INN Name: Aducanumab-avwa
g. Compendial Name: Not applicable.
h. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P05067 (A4_HUMAN) [BIIB037]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
761178/SN 0002	5/15/2020
761178/SN 0008	7/23/2020
761178/SN 0016	8/12/2020
761178/SN 0017	8/13/2020
761178/SN 0027	9/30/2020
761178/SN 0028	9/30/2020
761178/SN 0040	10/16/2020
761178/SN 0043	10/28/2020
761178/SN 0045	10/30/2020
761178/SN 0048	11/2/2020
761178/SN 0050	11/4/2020
761178/SN 0052	11/9/2020
761178/SN 0055	11/23/2020
761178/SN 0059	12/2/2020
761178/SN 0073	5/17/2021
761178/SN 0074	5/18/2021

Quality Review Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:
   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III	(b) (4)		3	Adequate	12/1/2020	None
	III			3	Adequate	12/1/2020	None
	III			3	Adequate	12/1/2020	None
	V			6	Deficient	5/14/2021	(b) (4)

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")
2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

   B. Other documents: IND106230

3. Consults: Dr. Thomas O'Conner (CDER/OTS, FDA emerging technology team) provided consult review on two novel process analytical technology (PAT) elements in the manufacturing process

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
(b) (4)	12/2/2020	Completed	Approval	Dr. Thomas O'Conner

4. Environmental Assessment of Claim of Categorical Exclusion: A categorical exclusion is claimed for the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c)

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761178 for ADUHELM manufactured by Biogen. The data submitted in this application are adequate to support the conclusion that the manufacture of ADUHELM is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:

    Biogen MA Inc.
    5000 Davis Drive
    Research Triangle Park, NC 27709, USA
    FEI: 3000719749

  - Drug Product:

    (b) (4)

    Biogen U.S. Corporation
    900 Davis Drive
    Research Triangle Park, NC 27709, USA
    FEI: 3010164829

    (b) (4)

- Fill size and dosage form:
  - Vial: 170 mg/1.7 mL and 300 mg/ 3mL

- Dating period:
  - Drug Product: 30 months at 2-8°C.
  - Drug Substance: (b) (4) months at (b) (4) °C
  - Stability:
    - For stability protocols: we have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release:
  - Yes, ADUHELM is a specified product and exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

ADUHELM (aducanumab-avwa) is indicated for treating Alzheimer's disease, an irreversible, progressive neurodegenerative disorder that slowly destroys memory and thinking skills. In the US, more than 5.8 million people are living with Alzheimer's disease. "...there is an urgent and unmet medical need for effective treatments for Alzheimer's disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease (FDA's position described in the briefing information of Peripheral and Central Nervous System(PCNS) Drugs Advisory Committee Meeting, November 6, 2020).

The OPQ assessment of manufacturing has identified that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The manufacturing process is robust for inactivation and removal of adventitious agents. The BLA is recommended for approval from product quality and sterility assurance perspectives. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of aducanumab-avwa at concentrations presented in the patient samples. ADAs were not assessed for neutralizing activity. The BLA assessment team concluded neutralizing antibody analysis was not necessary for approval of the BLA because the treatment emerging ADA positive rate is extremely low in the clinical studies and there was no observation of effect on ADA positivity on exposure or efficacy.

There are 4 product quality related and 1 immunogenicity assay related post marketing commitments. For each of these items, the information submitted in the BLA has provided sufficient level of assurance that these are not approvability issue. Additional study described in the product quality related PMCs will provide further assurance for consistently producing high quality product. The further study on the immunogenicity assay will inform any addition revision, if needed, is needed for the assay which will be used for testing clinical samples from the required confirmatory trial.

D. Recommendation on Phase 4 (Post-Marketing) Commitments (draft language)

1. Implement a validated product-specific host cell protein (HCP) assay in aducanumab drug substance manufacturing process. Submit the HCP method and method validation report in a supplement within 9 months of licensure.

2. Perform commercial shipping qualification studies for drug product and finished goods, and submit reports in a supplement within 8 months of licensure.

3. Provide the KTA bacterial endotoxin test method qualification data from Biogen MA and submit as a CBE-0.

4. Implement the bacterial endotoxins test for the (b) (4) and submit as a CBE-0.

5. Evaluate the potential for matrix interference from hemolysis and lipidemia in your antidrug antibody assay as a Post Marketing Commitment. Submit the final report within 6 months of licensure.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Potency	Efficacy	Intrinsic to the molecule, manufacturing process and storage	(b) (4)	Additionally, controlled by other CQAs that impact potency
Disulfide Structure	Efficacy, PK and immunogenicity	Intrinsic to the molecule and introduced during Manufacturing process		
N-linked Glycosylation: High Mannose	PK	Intrinsic to the molecule and introduced during Manufacturing process		
High molecular weight species	Efficacy, PK and immunogenicity	manufacturing process and storage		Stability-indicating

Low molecular weight species	Efficacy	manufacturing process and storage	(b) (4)	Stability-indicating
Charge variants	Efficacy and safety.	Intrinsic to the molecule. Manufacturing process and storage		Stability-indicating
Glycation	Efficacy	Intrinsic to the molecule. Manufacturing process		
Oxidized species	Efficacy and PK	Intrinsic to the molecule. Manufacturing process and storage can affect relative abundance		
Non glycosylated species	Efficacy	Manufacturing process		
FcRn binding	PK	Intrinsic to the molecule (b) (4)		
High order structure	Efficacy	Intrinsic to the molecule, manufacturing process		
Identity	Efficacy and Safety	Intrinsic to molecule		

DS - Drug Substance, DP - Drug Product, CE-SDS – Capillary electrophoresis sodium dodecyl sulfate, SE-HPLC – Size Exclusion Chromatography, icIEF – imaged capillary isoelectric focusing.

B. Drug Substance [aducanumab-avwa] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management*.

Category	Type	Risk	Introduction	Control Strategy	Other
Host Cell: CHO	Host cell	Host cell proteins, host cell DNA	(b) (4)	(b) (4)	A PMC to implement an assay that directly measure HCP in the manufacturing process was agreed on.
(b) (4)	Process related impurity	Patient safety	(b) (4)		n/a
	Process related impurity	Toxic			n/a

(b) (4)

- Description:

Aducanumab-avwa is a recombinant (IgG1) monoclonal antibody targeting aggregated soluble and insoluble forms of amyloid beta. It consists of two heavy and two kappa light chains connected by inter-chain disulfide bonds, with 12 intra-chain and 4 inter-chain disulfide bonds. Complementarity determining regions (CDR) sequences are in the heavy chain (residues 26-35, 50-66, and 99-113) and in the light chain (residues 24-34, 50- 56, and 89-97). Aducanumab-avwa has an molecular weight of approximately 146 kDa (excluding any post-translational modifications) and a pI of ~9.7. One N-linked glycosylation site is located at Asn304 on each heavy chain.

- Mechanism of Action (MoA):

Aducanumab-avwa is a human monoclonal antibody targeting aggregated soluble and insoluble forms of amyloid beta, which are pathophysiological features of Alzheimer's disease. Aducanumab-avwa reduces amyloid plaques which that accumulate in the brains of people with Alzheimer's disease through an antibody dependent microglia-mediated phagocytosis mechanism.

- Potency Assay: Biogen implements two potency assays in DS and DP release and stability.

Abeta binding assay: the Abeta binding assay is a competitive ligand binding assay to measure the binding of aducanumab to its ligand, beta-amyloid (1-42) peptide (Abeta peptide). Unlabeled reference standard/assay control/sample(s) compete with a europium-labeled aducanumab-avwa (Eu-Adu) for the opportunity to bind to Abeta peptide coated on a 96-well plate. The assay fluorescence signal is inversely proportional to the binding of unlabeled aducanumab-avwa to Abeta peptide. The binding of the sample/assay control to Abeta is compared to the binding of the reference standard to Abeta in order to generate a relative binding result.

FcγRIIa binding assay: the FcγRIIa binding assay is a biolayer interferometry based assay to measure the relative binding of the Fc portion of the aducanumab molecule to Fc gamma receptor IIa(FcRγIIa), which is covalently bound to glutathione-S-transferase (GST). The method is performed using anti-GST biosensors to create the binding complex. The binding of the analyte to the biosensor results in an increase in the thickness of the layer of protein bound to the biosensor tip, causing a nanometer shift in the light passed through the biosensor at two locations. The two light reflections produce an interference pattern proportional to the number of analyte molecules bound to the biosensor. The binding of the sample/assay control to FcγRIIa is compared to the binding of the reference standard to FcγRIIa in order to generate a relative binding result.

- Reference Materials (RM):

(b) (4)

- Critical starting materials or intermediates:

(b) (4)

(b) (4)

- Manufacturing process summary:

  Aducanumab-avwa DS is manufactured in Biogen MA Inc. Research Triangle Park, NC 27709, USA. (b) (4)

- Container closure:

  Aducanumab-avwa DS is stored (b) (4)

- Dating period and storage conditions: (b) (4) months at (b) (4) °C.

C. Drug Product, ABRILADA, Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

Category	Type	Risk	Introduction	Control Strategy
Sterility	Contaminant	Infections in patients, product stability	(b) (4) container closure failure	(b) (4)
Endotoxin	Contaminant	Adverse reactions in patients, DP failure	Accidental throughout process	
Appearance (Clarity and color)	General	Product stability	Formulation	

Osmolality	General	Product stability, patient discomfort	Formulation	(b) (4)
pH	General	DP failure, product stability	Formulation	
Visible particles	General	Safety and immunogenicity	Accidental throughout manufacturing process, CCS and stability	
Sub-visible particles				
Container closure	Process related impurities	Negative impact of leachables on product quality.	(b) (4) /storage	
Deliverable volume	General	Inaccurate dosing	(b) (4) /storage	
Identity	General	Medication error	Manufacturing process	
Protein concentration	General	Inaccurate dosing	Manufacturing process	
Excipient		Safety and product stability	Manufacturing process and formulation	

- Potency and Strength:
  - Vial: 170 mg/1.7 mL (100 mg/mL) or 300 mg/3 mL (100 mg/mL)

- Summary of Product Design:
  - ADUHELM (aducanumab-avwa) injection is supplied in a (b) (4) glass vial closed with a stopper and seal with a flip-off cap. The vials each contain a single dose of the drug product. Different color flip-off buttons are used to differentiate different dose presentations.

- List of Excipients:

Name of Excipient	Concentration
L-Histidine	(b) (4)
(b) (4)	
L-Methionine	10 mmol/L
Polysorbate 80	0.05% (w/v)

- Reference Materials: same as DS reference material.

- Manufacturing process summary: aducanumab-avwa DP is manufactured at (b) (4) or Biogen U.S. Corporation research Triangle Park, NC 27709, USA. The manufacturing process involves the following steps (b) (4) (b) (4)

- Container closure: (b) (4) clear glass vials with (b) (4) rubber stopper, and aluminum sealing with a flip-off button.

- Dating period and storage conditions: 30 months at 2 - 8°C.

- List of co-package components: None

D. Novel Approaches/Precedents: Biogen implemented several novel process analytical tools in the drug substance manufacturing process: (b) (4)

E. Special Product Quality Labeling Recommendations: ADUHELM should be diluted in 100mL 0.9% Sodium Chloride Injection, USP for administration. Do not use other intravenous diluents to prepare the ADUHELM diluted solution.

F. Establishment Information:

Overall Recommendation: Approval			
DRUG SUBSTANCE			
Function	Site Information	FEI Number	Assessment and Final Recommendation
DS manufacture; DS in-process control, DS/DP release, and stability testing; DS, MCB and WCB storage;	Biogen MA Inc. (Biogen RTP) 5000 Davis Drive , Research Triangle Park, NC, USA, 27709-4627	3000719749	Approve - Based on 704(a)(4)
(b) (4)			Approve - Based on Profile

	(b) (4)		
DRUG PRODUCT			
Function	Site Information	FEI Number	Assessment and Final Recommendation
		(b) (4)	Approve - Based on facility history, Waiver granted by OPMA/OBP
DP manufacturing; storage; Testing: Appearance (Color, Clarity); Endotoxin; Sterility;	Biogen U.S. Corporation 900 Davis Drive Research Triangle Park, NC 27709, USA	3010164829	Approve - Based on facility history, Waiver granted by OPMA/OBP
		(b) (4)	Approve - Based on Profile
			Approve - Based on Profile
			Approve - Based on Profile
			Approve - Based on Profile
			Approve - Based on profile
			Approve - Based on profile
			Approve - Based on profile
			Approve - Based on profile
			Approve - Based on profile
			Approve - Based on District File Review

G. Facilities: See the table in F. Establishment Information

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. (b) (4) Section 3.2.R Regional information
2. (b) (4), Section 3.2.S.2.5
3. Reference standard stability protocol, Section 3.2.S.5
4. Drug Substance stability protocol for ongoing studies, Section 3.2.S.7.1
5. Post-approval stability protocol of Drug Substance, Section 3.2.S.7.2

ii. Outstanding review issues/residual risk: none

iii. Future inspection points to consider: none

b. Drug Product

i. Protocols approved:

1. Drug Product stability protocol for ongoing studies, Section 3.2.P.8.1
2. Post-approval stability protocol of Drug Product, Section 3.2.P.8.2.2

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: none

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAOHENG N YAN
05/24/2021 09:59:53 AM

GIBBES R JOHNSON
05/24/2021 11:24:14 AM

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File (Drug Substance)

Application ID	BLA 761178
Submission Type	Original BLA
Drug Product Name	Aducanumab
Strengths	100 mg/mL
Dosage Form	Solution for Infusion
Administration Route	Intravenous Infusion
Indication	(b) (4) Alzheimer's disease (AD) (b) (4)
Applicant Name	Biogen Inc.
US License Number	1697
Application Type	351 (a)
Primary Reviewer	Zhong Li, Ph.D., Reviewer, CDER/OPQ/OPMA/DBM/Branch 1
Secondary Reviewer	Candace Gomez-Broughton, Ph.D., Branch Chief, OPQ/OPMA/DBM Branch 2 (microbiology) Thuy Nguyen, DHSc., Branch Chief, OPQ/OPMA/DBM Branch 1 (facility)
Goal Date	18 Dec 2020

Recommendation for Approvability:

- DS & DP Facility Assessment Recommendation: Approval
- The drug substance portion of this BLA was reviewed from a microbial control and product quality microbiology standpoint and is recommended for Approval.
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation:

Overall, the process is under adequate microbial control. (b) (4)

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Biogen MA Inc. (Biogen RTP) (FEI 3000719749), proposed for Aducanumab DS manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	_-
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process		_-

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original submission (0002)	2020-05-15
Response to IR (0028)	2020-09-30
Response to IR (0038)	2020-10-09

Application Submission Background

Reviewer's Comment: For Information

Aducanumab is developed for the treatment of Alzheimer's disease. Biogen's Large-Scale Manufacturing facility in Research Triangle Park, NC, RTP-LSM, is proposed for manufacture of commercial aducanumab DS. Two facilities are proposed for manufacture of commercial aducanumab DP: Biogen RTP-PF (NC, USA) and (b) (4)

MODULE 3.2.S

Module 3.2.S Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

S.1 General Information

Aducanumab is a recombinant human IgG1 monoclonal antibody that binds to aggregated forms of human amyloid beta. Aducanumab consists of two heavy and two kappa light chains connected by inter-chain disulfide bonds. The relative molecular mass of the molecule is 146 kDa (excluding any post-translational modifications). Aducanumab is manufactured using a recombinant CHO cell line.

Reviewer's Comment: For Information

S.2 Manufacture

S.2.1 Manufacturer(s)

Information about the facilities used for the manufacture and testing of aducanumab are provided. The manufacturing schedule for Biogen RTP-LSM facility responsible for production of the aducanumab DS is provided in the reviewer's guide.

Reviewer's Comment: Refer to *Facility Assessment* section in this review memo for details.

Zhong Li

Digitally signed by Zhong Li
Date: 11/06/2020 11:54:41AM
GUID: 5452326f000475beaec6af628762212a

Thuy Thanh Nguyen

Digitally signed by Thuy Thanh Nguyen
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GUID: 5256cce70002b21dd4c17f3ef09b075c

Candace Gomez-Broughton

Digitally signed by Candace Gomez-Broughton
Date: 11/06/2020 01:27:50PM
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